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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,878	10/15/2001	Marsha A. Moses	CMZ-130	3811

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,878	MOSES ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *3-5, 8, 29-31, 34, 49-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,6,7,10-28,40-48 and 77-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Jan 28, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants election of Group I, and applicants election of the species of breast cancer, both elections without traverse.

Claims 1-80 are pending. Claims 3, 29, 49-76, drawn to non-elected inventions, are withdrawn from consideration. Claims 4, 5, 8, 30, 31, 34, drawn to non-elected species, are withdrawn from consideration. Claims 1, 2, 6, 7, 9-28, 32, 33, 35-48, 77-80 are examined on the merits. Claims 77-80 are examined to the extent that they read on the methods of claims 1 and 27. Claims 1 and 27 are examined to the extent that they read on cancer as a tissue remodelling-assoicated condition. After reconsideration of the species election in light of the prior art, the species of genito-urinary tract and gastrointestinal cancer will be examined with breast cancer at this time. Claims 7 and 33 are examined to the extent that they read on the elected species of breast cancer , genito-urinary tract cancer and gastrointestinal cancer. Claims 10 and 36 are included with this species because breast cancer is commonly metastatic to the bone.

Priority

Acknowledgement is made of applicants claim to an earlier effective filing date through provisional application 60/240,489 filed October 13, 2000. the specification also states that the instant application "is related to" application 08/639,373, filed on April 26, 1996, application 09/469,637, US 6,037,138. Upon review of each of these applications, it was noted that NGA lipocalin was not disclosed until the '489 provisional application. All of the instant claims are reliant upon NGAL/lipocalin either in whole (claims 27, 28, 30-33, 36-48) or in part (claims 1, 2, 4-7, 10-26, and 77-80). Thus, the statement "related to" does not imply an effective filing date earlier than the provisional application. It is also noted that the "related to" applications were not set forth in the Oath/Declaration. Thus, applicant is not claiming the benefit of domestic priority to said applications.

Specification

The incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure on page 1 to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration

executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6, 7, 9-28, 40-48, 77-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high molecular weight" in claims 1, 11, 15, 19, 77-80 and the term "low molecular weight" in claim 41 is a relative term which renders the claims indefinite. The term "high" or "low" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 10-28, 32, 33, 36-48, 77-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant method claims are dependent upon the identity of molecules comprised within a "high molecular weight complex". The specification discloses complexes comprising matrix metalloproteinases comlexed to tissue inhibitors of matrix metalloproteinases. The specification further teaches that when the matrix metalloproteinase is MMP-9 (also known as gelatinase B, 92 KDa), the specific lipocalin known as neutrophil gelatinase B associated lipocalin can also be present in the complex. The specification identifies MMT-9 as a serine protease, however, many other serine proteases are known in the art which are not metalloproteinases. The instant claims are reliant upon the identity of a large genus of high molecular weight enzyme complexes which are not limited in structure or specific function (note: the recitation of "enzyme" does not imply a specific function but encompasses any catalytic activity carried out by a protein). The specification provides a written description of matrix metalloproteinases complexed with tissue inhibitors of matrix metalloproteinases, and in the case of matrix metalloproteinase -9, further complexed with NGAL. However, this written description does not serve to adequate describe the claimed genus of enzyme complexes because the genus comprises enzyme complexes having subunits that have no resemblance structurally or functionally with the instant disclosed MMP/TIMP or MP-TIMP/NGAL.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe the genus of a high molecular weight enzyme complex in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any enzyme or serine protease that is not a matrix metalloproteinase, nor does the specification provide any description of a enzyme complex comprising a tissue inhibitor of a matrix metalloproteinase that is complexed with an enzyme which is not a matrix metalloproteinase. Although the specification discloses a enzyme complexes comprising MMP and TIMP and an enzyme complex comprising MMP-9, TIMP and NGAL this does not provide a description of the enzyme complexes that would satisfy the standard set out in Enzo.

The specification also fails to describe the enzyme complexes by the test set out in Lilly. The specification describes enzyme complexes limited to MMP and TIMP and therefore fails to describe a "representative number" of such species that would fall within the genus of enzyme complexes and enzyme complexes limited only to serine proteases, MMPs and TIMPs. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus", wherein said structural features would be present in the wider genus of serine proteases or "enzymes".

Thus, the specification does not provide an adequate written description of the genus of "enzyme complex" that is required to practice the claimed invention. Since the specification fails to adequately describe the product on which the claimed methods rely, it also fails to adequately describe the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-7, 10-26, 40-48, 77-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Moses et al (Cancer Research, 1998, Vol. 58, pp. 1395-1399) as evidenced by Yan et al (Journal of Biological Chemistry, 2001, Vol. 276, Vol. 40, pp. 37258-37266).

Moses et al disclose a method of detecting breast carcinomas by means of detecting high molecular weight complexes comprising MMPs in the urine (Table 2, page 1397 and Figure 1, page 1396) by means of a zymogram containing gelatin (page 1396, under the heading "Data Collection and analysis"). Moses et al disclose that the urine was dialysed before gel electrophoresis (page 1395, second column, lines 8-12 of the section "Sample Preparation and Substrate Gele Electrophoresis". Moses et al disclose that detection the 125 kDa molecular weight complex in the urine was indicative of breast cancer (page 1396-1397, bridging sentence and page 1398, second column, lines 39-49).

Yan et al provides evidence that the 125 kDa complex disclosed by Moses et al comprised gelatinase B (MMP-9) and a dimer of the neutrophlil associated gelatinase lipocalin (NGAL) (page 37264, first column, lines 53-58). Thus, the detection of the 125kDa complex as disclosed by Moses comprises the detection of MMP-9 complexed with two molecules of NGAL.

Claims 1, 2, 6, 7, 9-12, 46, 77-80 are rejected under 35 U.S.C. 102(b) as being anticipate by the abstract of Black et al (Clinical Cancer Research, Feb 2000, Vol 6, pp. 467-473).

The abstract teaches a method for diagnosing breast cancer comprising detecting levels of PSA complexed to alpha-1 chymotrypsin and detecting levels of free PSA in serum. The abstract teaches that an established immunoassay was carried out to detect total PSA(which includes complexed PSA) in the serum of women with no known malignancies, benign breast disease and breast cancer. The abstract discloses that free PSA shows high diagnostic specificity for breast cancer, and thus fulfills the specific limitation of claim 1, drawn to correlating the presence or absence of the high molecular weight enzyme complex with the presence or absence of cancer, because women with high levels of free PSA would also have high levels of complexed PSA. The disclosure of breast cancer fulfills the specific embodiment of claim 10, drawn to a cancer which affects cells of bone or of hematopoietic origin, because breast cancer is commonly metastatic to the bone marrow.

Claims 1, 2, 6, 7, 9, 11-13, 17-20, 25, 26, 46, 48 and 77-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533)

Zucker discloses a non-invasive method of diagnosing metastatic genito-urinary tract cancer and gastrointestinal cancer comprising analyzing plasma for the presence of MMP-9 and TIMP-1/MMP-9 complexes by an ELISA immunoassay (page 18). Zucker discloses a non-invasive method of diagnosing breast cancer or gastrointestinal cancer comprising measuring by an EILSA assay MMP-2 complexed with TIMP-2 in plasma (page 15 to page 16, line 6). Zucker discloses that free TIMP-2 has a molecular weight of 22kDa, but is found in complexes

of MMPs having molecular weights of up to 150 kDA (page 7, lines 29-34), thus fulfilling the specific embodiment of claim 25.

Kolkenbrock et al disclose that gelatinase B (MMP-9) can exist in three forms: monomer, homodimer and monomer/lipocalin complex. Kolkenbrock et al disclose that about 50% of the monomer/lipocalin complex was found further complexed to TIMP-1 (abstract, lines 1-7). Kolkenbrock et al disclose that gelatinase B exhibits three bands on SDS-gel electrophoresis of 220, 130 and 92 kDa. Kolkenbrock et al disclose that the 92 kDa and the 220 kDa forms represent the monomer and the homodimer of the gelatinase B. Kolkenbrock et al t disclose that the 130 kDa form is the monomer complexed with a 25 kDa protein having homology to rat alpha-2-microglobulin protein which was determined to be lipocalin (page 530, first column, lines 28-29). An alternative name for this 25 kDa protein is neutrophil gelatinase associated protein (NGAL) as further evidenced by the abstract of Kjeldsen (Journal of Biological Chemistry, 1993, Vol. 268, pp. 10425-10432). Kolkenbrock et al discloses that TIMP-1 was exclusively bound to the monomer/lipocalin complex (page 532, first column, lines 12-17), thus providing evidence that the MMP9-TIMP-1 complex detected in the method of Zucker further comprised lipocalin because the binding of TIMP-1 requires the complex of MMP-9 and TIMP-1, rather than MMP-9 alone.

The disclosure of the MMP-2/TIMP-2 complex by Zucker fulfills the specific embodiments of claims 78-80, because said claims are negating complexes comprising gelatinase B (MMP-9) but read on complexes of MMP-2 (gelatinase A) complexed with TIMP-2

The disclosure of the MMP-9/TIMP-1 complex fulfills the specific embodiments of claim 77 because the molecular weight of the complex would be representative of the MMP-9/lipocalin/TIMP-1 complex which is 130 kDa as evidenced by Kolkenbrock et al.

The disclosure of Zucker on the detection of MMP-9 in addition to MMP-9/TIMP-1 inherently fulfills the specific embodiments of claims 19 and 20, drawn to an enzyme complexed with itself in a dimer because Kolkenbrock et al disclose that gelatinase B forms homodimers. thus, it would be inherent in the method of Zucker that both monomer and homodimers of MMP-9 would be detected. the disclosure of Zucker on the detection of MMP-9 rather than MMP-9 complexed with TIMP-1 fulfills the specific embodiment of claim 26 because Kolkenbrock et al disclose that MMP-9 exists in a monomeric-lipocalin form which would have the molecular

weight of the 25 kDa lipocalin and MMP-9 (92 kDa), and thus a molecular weight between 115 to 125 kDa.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28, 32, 33, 35-37, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (US 6,610,484) in view of Stoesz et al (International Journal of Cancer, 1998, Vol. 79, pp. 565-572).

Hung teaches a non-invasive method for facilitating the diagnosis of cancer in a subject comprising obtaining material from a breast duct and identifying markers in the ductal fluid (abstract). Hung teaches that a marker can comprise a serine protease (column 6, line 63), collagenases, metalloproteinases and TIMPs (column 11, lines 40-45). Hung does not teach the neutrophil gelatinase associated lipocalin as a marker which can be detected in ductal fluid for the diagnosis of breast cancer.

Stoesz et al teach that NGAL expression by breast carcinomas was correlated with other markers of poor prognosis such as estrogen and progesterone receptor status and high proliferation (abstract, lines 19-23). Stoesz et al teach that NGAL accounts for nearly 0.1% of

the total soluble protein produced by some breast tumors (page 571, second column, lines 29-33). Stoesz et al teach that NGAL is secreted from breast carcinomas into normal ducts and that NGAL levels were significantly higher in smaller tumors (page 571, lines 23-26) suggesting a utility of NGAL in the detection of early tumors. Stoesz et al teach that NGAL may be detected in the breast fluid of some women having breast cancer (page 571, second column, lines 26-29).

It would have been prima facie obvious at the time the invention was made to obtain a sample of breast duct fluid form a patient and detect NGAL in said fluid, and correlate the presence of NGAL in said fluid with the presence of breast cancer. One of sill in the art would have been motivated to do so by the teachings of Stoesz et al on the likelihood that NGAL is secreted into normal ducts by early tumors. One of skill in the art would be motivated to detect early tumors, especially tumors carrying markers for poor prognosis in order to impose therapeutic intervention. The disclosure of breast cancer fulfills the specific embodiment of claim 36 drawn to a cancer which affects cells of bone or of hematopoietic origin, because breast cancer is commonly metastatic to the bone marrow.

Claims 1, 2, 6, 7, 9, 11-13, 17-20, 25, 26, 46-48 and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533) in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pp. 115-122).

The combination of Zucker et al and Kolkenbrock et al render obvious a method of detecting the enzyme complexes by means of an ELISA assay as applied to claims 1, 2, 6, 7, 11-13, 17-20, 25, 26, 46, 48 and 77-80. the combination does not teach a radioimmunoassay.

Kerr and Thorpe teach the common techniques of radioimmunoassay and ELISA assay (pp. 115-122) as methods of detecting proteins by binding to antibodies carrying a detectable label. Kerr and Thorpe teach that labeling with radioisotopes is usually easy and the conjugates are particularly suitable for many immunochemical procedures (page 115, lines 1-2) It would have been prima facie obvious at the time the invention was made to use a radioimmunoassay for the detection of the enzyme complexes. One of skill in the art would have been motivated to do so by the teachings of Kerr and Thorpe on the easy of radiolabeling antibodies and using the labeled antibodies in immunochemical procedures. .

Claims 1, 2, 6, 7, 9, 11-13, 17-20, 25, 26, 43-46, 48 and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, Vol. 377, pp. 529-533) and Moses et al (Cancer Research, 1998, Vol. 58, pp. 1395-1399).

Claims 43-45 are drawn to detection of the enzyme complexes by zymography. The combination of Zucker and Kolkenbrock et al render obvious the detection of the complexes by immunochemical methods. Neither reference teaches the detection of the complexes by zymography.

Moses et al teach that zymography detects a series of enzyme species in a single evaluation and provide additonal novel data on cancers which display characterisitc zymographic patterns (page 1398, second column, lines 39-46). Moses et al teach the zymogram substrate of gelatin (page 1395, under the heading "Sample Preparation and Substrate Gel Electrophoresis, lines 13-14).

Tsuda et al teach that there is a correlation between gelatinase B enzyme activity and the metastatic potential of tumors (page 38, second column, lines 14-18).

It would have been prima facie obvious at the time the invention was made to detect the gelatinolytic activity of MMP complexes isolated from the plasma of cancer patients. One of skill in the art would have been motivated to do so by the teachings of Moses et al demonstrating the utility of the method in detecting the novel 125 kDa high molecular weight species, and the teachings of Tsuda et al correlating the enzymatic activity of MMP-9 with metastatic potential

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 6, 7, 9-28, 32, 33, 35-48, 77-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being anticipated by claims 130, 149-180 of copending Application No. 09/469, 637.

The claims of the '637 application are drawn to non-invasive methods that facilitate the diagnosis of cancer of epithelial origin in a subject, said methods comprising the detection of a matrix metalloproteinase having a molecular weight of 50 kDa to greater than 150 kDa in a urine sample, which is a species which anticipates the current claims drawn to a enzyme complex because the detection of a matrix metalloproteinase having a molecular weight of up to 150 kDa or above reads on the detection of the MMP-9/NGAL (115 kDa) and MMP-9 homodimer (220 kDa)

This is a provisional obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.